COVID-19 and the COVID-19 Vaccines

COVID-19

1. **How many cases of DBA patients having COVID-19 have been reported to the DBAR? Are there any data available regarding:**
   a. patient demographics?
   b. outcomes and hematological implications?
   c. treatments?
   d. complications?

Initially we had 4 cases of COVID-19 reported to the DBAR. One child was less than 1 year old and the other 3 individuals were between 23-36 years of age. All 4 individuals did not require any hospitalizations or experience any complications. We are collecting more patients as the pandemic has continued. We have not had many cases – most likely due to patients and their families keeping safe with masks, social distancing and great hand hygiene.

2. **Have we learned if being iron overloaded is a risk factor?**

Of course, we have no studies specifically regarding iron overload and COVID, but we do believe iron overload may pose some increased risk. Iron overload may be affecting your endocrine organs which could decrease your immune system. Additionally, iron overload in your bone marrow may leave you with less reserve and therefore the virus could suppress your counts. Overall, when you are iron overloaded, your general health and organ function are potentially worse, making any illness more dangerous for you.

3. **Are there any data from other related rare disorders, either bone marrow failure syndromes or immunological disorders that may be helpful?**

Dr. Vlachos is working with other institutions from the North American Pediatric Aplastic Anemia Consortium to look at this question. The initial survey of over 25 institutions and over 1000 patients only had 4 positive patients with aplastic anemia and Fanconi anemia. These patients also have done well with COVID-19. We are repeating this survey in over 40 institutions and are looking to report these data.

4. **What are your concerns with the "new strains?" Reports indicate the UK strain is more transmittable and possibly more lethal. Some evidence supports an increase in pediatric cases and hospitalizations. If this proves true, what measures should we take to protect our children and ourselves?**

All viruses have the ability to mutate. As long as COVID-19 is active it will continue to develop new strains. The best way to combat this is for as many people as possible to get vaccinated. If the virus cannot infect a person, then it slows down its replication. There is evidence that the current COVID-19 vaccines have protection against some of these strains. If you are vaccinated then you have less chance of spreading the disease to your children who cannot be vaccinated yet. Even after vaccination though the best way to protect yourselves and your children is to continue to wear masks, social distancing, and hand hygiene in public.

VACCINATIONS

1. **Can you please explain the differences between the new mRNA vaccines (Pfizer and Moderna) and the more "traditional" vaccines like the adenovirus-based vaccines (Johnson & Johnson and AstraZeneca)?**

The goal of a vaccine is to train the immune system to recognize a disease so when you are exposed to the disease or actually get the disease, your immune system will respond to knock it out quickly. We normally get the flu vaccine or the tetanus vaccine which are both "killed" vaccines – that is, they have a small non-harmful particle of the actual disease in the vaccine. Our body sees that and makes an immune response to that piece. Other vaccines like the chicken pox vaccine contain "live" viral particles to do the same.

Messenger RNA, or mRNA, is the instruction booklet to making proteins. With mRNA vaccines, the mRNA to make a piece of the COVID-19 virus, namely the spike protein, is injected into the person being vaccinated. The mRNA enters into our immune cells in a space of the cell called the cytoplasm. There, the mRNA instructs the ribosomes (the protein-making factory of the cell) to make the spike protein. The spike protein then sits on the surface of the cell. Our immune system recognizes that the spike protein isn't supposed to be there, and it triggers our body to have an immune response and make antibodies against the spike protein of the COVID-19 virus.

It is important to note that mRNA does not cause an actual COVID-19 infection. It is not a "killed" piece of the virus nor a "live" virus. Additionally, the mRNA sits in the cytoplasm and never enters the cell's nucleus where our DNA lives. The mRNA never gets into the area where our DNA is located and therefore cannot integrate into human DNA that is, it cannot change our DNA. After the mRNA has instructed the ribosomes to make the spike protein, the body then completely breaks down the mRNA within a matter of hours and it is no longer in our body. What is left in our body are the antibodies against the spike protein of the COVID-19 virus.

Adenovirus-based vaccines use another virus, namely the adenovirus, with the DNA for making the spike protein inserted in it. Adenovirus is a common virus associated with the common cold and mild gastrointestinal effects. Researchers are able to take the regular adenovirus and shut off all the genes that make it replicate, so that when it is injected into you as a vaccine you will not become ill from the adenovirus itself. Instead, they insert into the adenovirus the DNA that codes for the COVID-19 spike protein. After vaccination the adenovirus enters into your immune cells and goes inside the nucleus. Your cells use the DNA codes from the vaccine to produce mRNA. The mRNA then tells the ribosomes (the protein-making factory) to make the spike protein which then sits on the surface of the cell. Our immune system recognizes that the spike protein isn't supposed to be there and it triggers our body to have an immune response and make antibodies against the COVID-19 spike protein.

One of the potential downfalls to the adenovirus-based vaccines is that many of us have been exposed to adenovirus before as it is one of the common viruses. There is concern that if your body already has antibodies to the specific strain of adenovirus that is used to deliver the DNA, then the antibodies would render the vaccine ineffective.

So the main difference here is the mRNA vaccine is directly delivering the mRNA to our cells that will tell the ribosomes to make the spike protein. However, in the adenovirus-based vaccine the vaccine enters into the nucleus and the DNA then makes the mRNA which then makes the spike protein.

Most Frequently Asked Question:

2. **Are there any reasons a DBA patient should NOT receive the vaccination – either the approved mRNA vaccines or the adenovirus-based COVID vaccine?**
   Questions were asked specifically regarding how the vaccine may affect or be affected by:
   a. neutropenia
   b. low platelets (There is a speculative report that a healthy doctor died after his platelets fell to 0.)
   c. steroid use
   d. transfusions and chelation
   e. post-transplant patients
   f. compromised immune system – ie low T cells or B cells
   g. low IGG
   h. RPL35a
   i. low bone marrow cellularity
   j. severe food allergies
   k. asthma

All patients with DBA are generally recommended to get vaccinated. The only contraindication to vaccination is if you have had a severe allergic reaction to the first dose of the vaccine or have a known allergy to polysorbate used in the vaccine preparation. Those patients who have known history of severe allergic reactions should still get the vaccine but will be monitored for 30 minutes after the dose, rather than the 15 minutes that is standard. Those patients with compromised immune systems, neutropenia, or who are post-transplant, or have a low IgG, etc. are all recommended to get the vaccine. Given this is NOT a live viral vaccine, it is safe for all immune compromised groups.

With regards to the case with low platelets, the patient developed immune thrombocytopenia and unfortunately died of a brain hemorrhage (bleeding in the brain) due to the low platelets. Immune thrombocytopenia is a disease caused by a patient's own immune system making antibodies against the patient's own platelets. This can be diagnosed after viral infections in young children and has been noted in other autoimmune diseases like lupus and Crohn's disease. It can also be caused by the COVID-19 infection as well. It has been extremely rare after the COVID-19 vaccine, and this is the only fatal case reported.

3. **Is the DBAR collecting data on DBA patients who have received any of the COVID vaccines to date? Is there any information to share or recommendations?**

The DBAR is collecting data on anyone with DBA who has had a COVID-19 infection. We do hope that patients continue to complete the COVID-19 Questionnaire (found on the www.DBAR.org website) if they have been infected. We will be adding to that survey to keep track of patients with DBA who have received the vaccine, to document which vaccine and side effects noted, if any. We are collecting these data and encourage you to reach out to the DBAR to inform us of your vaccination status.

4. **Do the new vaccines using mRNA pose any possible complications specifically for a bone marrow failure patient?**

The mRNA vaccines do not pose any specific complications for a bone marrow failure patient, because the mRNA never gets inside the nucleus of the cell, where our DNA is stored. Also, after the mRNA instructs the body to make the spike protein, the mRNA is rapidly removed from the cell (degraded).

5. **Are there any instances when either the Pfizer vaccine or the Moderna vaccine is preferred over the other?**

No one vaccine is preferred over the other. They both have similar efficacy and they are both mRNA vaccines. The best vaccine for you is the one that you have access to!

6. **How can we be confident that there will not be long term effects (ie cancer, neurological issues, heart disease, reproductive issues) from the new mRNA vaccines? With decades of experience using viral vector vaccines vs. the new mRNA vaccines, might it be "safer" to receive an adenovirus-based vaccine?**

While mRNA vaccines have not been used in clinical practice before, they have been studied extensively for many years. It is not a new technology for a vaccine. We do not anticipate any long term side effects from the mRNA vaccine for two reasons, specifically. First, the mRNA never enters the nucleus of the cell, which is where our DNA is stored so it never has access to our DNA. Secondly, the mRNA is broken down and removed as soon as it finishes telling the body to make the spike protein. The mRNA does not stick around in our body and therefore we would not anticipate any long term side effects as the vaccine is essentially cleared out, leaving behind only the immune response which are the antibodies against COVID-19.

The Johnson and Johnson vaccine is now available which is an adenovirus-based vaccine. It has had some increased side effects reported as it is a single vaccine. In some countries it is only being given to the younger population.

7. **If we are able to shelter, should we wait to vaccinate for a year, or possibly longer, to assess potential side effects of the vaccines?**

We do not recommend waiting to receive your vaccination. Even if you are very strict with COVID-19 precautions you still have to be near other individuals at the grocery store, at work, at the gas station, at the doctor's office and the pharmacy, etc. It is important for all of us to get vaccinated for the development of herd immunity. As we see new strains of the COVID-19 virus, it is even more important to vaccinate. The more people that are vaccinated, the less chance the virus has to replicate. The virus can only mutate during active replication, so if we stop the replication we can help prevent new mutated strains from developing. Again, because the mRNA does not incorporate into our DNA we do not anticipate any long term side effects. Unfortunately, we are starting to see long term complications from active COVID-19 infection.

8. **Are the adenovirus-based vaccines considered "live" vaccines? Are they safe for patients on prednisone or patients considered immunocompromised? For example, if it is recommended to not receive the MMR or varicella vaccines, would the adenovirus-based vaccines for COVID-19 also be contraindicated?**

Neither the mRNA nor the adenovirus-based vaccines are considered "live" vaccines. The adenovirus-based vaccines are not administering the actual COVID-19 virus, instead they are instructing our immune cells to make the spike protein found on the COVID-19 virus which then stimulates an immune response. They are considered safe for immunocompromised patients.

9. Is there a titer available to check if a person mounted an appropriate response to the vaccination?

Traditional COVID-19 antibody tests detect antibodies formed after an active COVID-19 infection. These antibody tests will not necessarily detect if you have formed antibodies after vaccination. After vaccination with both Pfizer and Moderna vaccines the antibodies you form are only to one part of the virus: the spike protein. Many of the antibody assays are not specific for antibodies to the spike protein at all and would be negative even if vaccination was successful and protective.

10. Is the current antibody test a good measure of response to the vaccine? Is there a group of patients that may benefit from checking a titer, if available?

At this time COVID-19 antibody testing is only recommended to see if you have had COVID-19 in the past, and is not a marker of response to the vaccination. Therefore, we would not recommend this testing at this time.

11. When do you expect vaccines will be available for children?

The Pfizer vaccine can be given to patients down to 16 years of age. At this time there is no COVID-19 vaccine for children under 16 years of age. There are ongoing clinical trials for testing between ages 12-18 years old, but they are not yet completed. There have been no trials started in younger children, so we expect it to be some time before the vaccine is available to them.

12. Have there ever been vaccines deemed safe for adults, but not for children?

Most vaccinations are meant to improve child health. However, for the pediatric versions of vaccines for hepatitis A and B, children receive lower doses of the vaccines than adults as children can generate an immune response with lower doses. With diphtheria and pertussis vaccines, adults actually get a smaller dose than children because they are more likely to experience side effects of those vaccines. The shingles (zoster) vaccine is only recommended to adults over age 60 years.

13. Would you be comfortable giving the vaccine to DBA patients who meet the current age eligibility, but are young (16-18 years old)?

Yes, at present only the Pfizer vaccine has currently been tested in children as young as 16 years of age and did not show safety concerns. We would recommend children as young as 16 years getting vaccinated.

14. Should parents of DBA patients be vaccinated? Is either the mRNA or viral vector vaccine preferred?

The parents of DBA patients should certainly be vaccinated. Since vaccines are not available for our children right now, the best way to protect them is by vaccinating everyone around them. If those around them are vaccinated, they are less likely to transmit the virus even if they become infected, thus offering our children the greatest protection.

15. Is there any research that you know of regarding the vaccine and breast feeding? Specifically, if a "healthy" mom receives the vaccination and her nursing child with DBA is on high dose steroids?

The American College of Obstetrics and Gynecology as well as the World Health Organization both recommend COVID-19 vaccination is safe in breastfeeding mothers. Women who are breastfeeding or pregnant were not included in the vaccine clinical trials so there is no real data at this time. However, the mechanism of action of the mRNA vaccines and data from other vaccine administration to breastfeeding mothers do not indicate an increased risk. There is no live virus in the mRNA vaccines so you cannot get COVID-19, or give your baby COVID-19, by being vaccinated. After you get the vaccine, the mRNA is removed from your body quite quickly and therefore unlikely to get into any breast milk. However, even if some of the vaccine were to make it to the breast milk, the baby would then have to digest it through their stomach, and we know that the vaccine is not effective as an oral medication.

Importantly, after vaccination, your body develops antibodies to protect against COVID-19. These antibodies can be passed through the breast milk to the baby and therefore newborns of vaccinated mothers who breastfeed may benefit from these antibodies.

16. Are there any known factors that may contribute to who has more severe reactions to the vaccines?

Typically, we are seeing that younger individuals are having more side effects within 24 hours after the second dose of vaccine administration including fever, headache, chills, and sore muscles. However, all of these side effects are self-limited and respond nicely to Tylenol. There is also some thought that those who have already had a COVID-19 infection will have a stronger immune response to even the first dose of the vaccine and experience some of the side effects at that time, including headache, fever, chills, etc. Again, these side effects are self-limited and typically resolve within 24-48 hours.

TREATMENTS

1. What are the current treatment options for COVID-19 that you are aware of?

Per the National Institute of Health COVID-19 Treatment Guidelines: Remdesivir is the only drug approved by the FDA for treatment of COVID-19. It is an anti-viral drug that is recommended for both adult and pediatric patients that are hospitalized because of COVID-19 and require oxygen. Dexamethasone is recommended for hospitalized patients that require oxygen and has shown the greatest effect in those that require mechanical ventilation.

There are also COVID-19 monoclonal antibody treatments such as Bamlanivimab and Casirivimab/Imdevimab (REGEN-COV™). These are antibodies made against the COVID-19 spike protein. These prophylactic treatments bind to the spike protein and lead to a decrease in the viral load and slow down the replication of the COVID-19 virus. These that are NOT recommended for use in hospitalized patients. They are available under Emergency Use Authorization in NON-HOSPITALIZED patients aged 12 years and older that are at risk of severe progression of disease. These are effective if you are not as sick with COVID-19 yet – to prevent you from getting sicker.

Patients aged 12 years and older are considered high risk if they have any one of the following:

- obesity (BMI greater than 35)
- chronic kidney disease

- diabetes
- immunocompromising condition
- receiving immunosuppressive treatment
- are 65 years of age and older
- are 55 years of age and older with cardiovascular disease, hypertension or chronic obstructive pulmonary disease (COPD)

For children less than 12 years of age, high risk is defined as:

- BMI greater than the 85th percentile
- sickle cell disease
- congenital or acquired heart disease
- neurodevelopmental disorders
- asthma
- reactive airway disease that requires daily medication for control
- tracheostomy
- gastrostomy

2. Are there any treatments that should be used, or should not be used, with DBA patients?

DBA patients should follow the routine treatment guidelines for COVID-19. Remember patients on chronic steroid therapy and those with iron overload, or complications of iron overload such as cardiac dysfunction or diabetes, should be eligible for COVID-19 antibody treatment if they contract COVID-19 and are not hospitalized.

3. The NIH has recently dropped its recommendation against the use of Ivermectin. Do you have any reservations with the use of this drug in DBA patients?

There are no data about the use in Ivermectin specifically in DBA. It is a treatment for parasitic infections and there is no information for its clinical effectiveness in COVID-19 infection which is a virus illness. Thus, we do not recommend the use of Ivermectin to treat COVID-19 infections.

4. Since most doctors are unfamiliar with DBA, what is important information we should give the ER doctor, or treating doctor, if a child or adult with DBA tests positive or has symptoms? What important information should they be aware of to properly care for a DBA patient with COVID-19?

Given the rarity of DBA it is important to be your own advocate when it comes to your care. As always, we are willing to speak to any doctor about DBA to help educate them about this disease and ensure you are getting the best care possible. It would be important to let a treating physician know what your baseline hemoglobin is. If you are transfusion dependent, let the doctor know when your last transfusion was. You should certainly have your hemoglobin checked if you are diagnosed with COVID-19 to ensure you have not had a drop in your hemoglobin necessitating a blood transfusion. It is important to let your doctor know each medication you are taking including iron chelators as they can have kidney or liver toxicity, and in the setting of severe COVID infection kidney and/or liver function could be compromised. Patients on steroid therapy should also make the doctor aware of the dose of steroids and may need an increase in the dose during the COVID infection.

5. **Do you advise any vitamins or supplements be taken prophylactically? Specific questions were asked about Vitamin D, Zinc, Vitamin C, and aspirin based on reports.**

We do not recommend any prophylactic supplementation unless you are known to be deficient in one of the vitamins. Specifically, we caution the use of Vitamin C in patients with DBA on transfusion therapy as vitamin C can increase absorption of iron.

6. **Often, we are told to stop chelating if we are ill. In Iran, there is a clinical trial using Desferal to possibly reduce the severity of COVID-19 manifestations. Should we continue to chelate with Desferal if we have, or suspect, COVID-19?**

Illness, especially viral illness, can increase your liver function tests. Chelation can also make liver and kidney function worse especially during an illness. Therefore, chelation often needs to be stopped during a serious viral illness as the liver may get more inflamed. The oral chelation medications (Exjade and Jadenu) can do this more than subcutaneous Desferal. It is important to check your liver function tests if you are ill to see if they are elevated and hold the medication until they return to your baseline. The increase in liver enzymes may be worse if you already have iron overload.

GENERAL QUESTIONS

1. **Can you please address the urgency, frequency and necessity of "routine" testing and imaging during the pandemic? If a patient is status quo, should eye tests, hearing tests, bone marrow aspirates/biopsies, done density and MRI imaging be put on hold, especially if a family must travel for the testing? What and when should testing and imaging NOT be delayed?**

Healthcare right now is different depending on where you live. Staying home and away from the hospital may be the safest option at this time. If all has been status quo, routine tests such as hearing, eye exams, bone density, etc. can be delayed 6 months to 1 year, if needed. Hopefully, this will allow for greater dissemination of the COVID-19 vaccine and increased immunity in the community. That being said, many healthcare institutions have gone to great lengths to ensure the safety of their patients during this time. We encourage you to seek medical care for anything that may be "different" than your baseline and do not delay seeking care for fear of being exposed to COVID-19 in the hospital. Delaying care could worsen your overall health and lead to worsening complications that actually warrant an admission to the hospital. Please do not let prescriptions go unfilled, and continue chelation and blood transfusions as you have previously done. When possible, you can opt for telehealth visits with your provider and some hospitals have options such as drawing labs at your home. If there is ever a question about the necessity of a test, discuss with your physician or with the DBAR team and we can help guide you.

2. **It seems like many people have COVID fatigue despite the recent increases in cases and deaths. Restrictions, lockdowns, and attitudes vary in every state and country. Messaging from state and local officials is inconsistent, and often conflicting. Ontario has issued stay-at-home orders, and some countries are in lockdown. US governors, mayors and local supervisors are all saying something different. I want to survive this pandemic and refuse to take it lightly. What are some metrics that we should be following to decide the risk level in our area? Hospitalization rate? Infection rate? New cases?**

Infection rate is likely the best statistic to follow at this time to determine the risk in your area. Following the rates of infection would allow you to help determine your risk of COVID-19 exposure in the community. While hospitalization rates are important, the number of cases in your surrounding area is what can directly affect you and your potential exposure.

3. What are the most reliable resources to keep ourselves educated about treatments and vaccines?

The Center for Disease Control and Prevention (CDC) as well as the World Health Organization (WHO) both have informative websites and are 2 reliable sources.

https://www.cdc.gov/coronavirus/2019-ncov/index.html

https://www.who.int/emergencies/diseases/novel-coronavirus-2019